Remarks

I. Status of the Claims

Reconsideration of this Application is respectfully requested.

Claims 50-59 and 74-76 are pending in the application, with 50 being the independent claim.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

II. Summary of the Office Action

In the Office Action dated August 2, 2004, the Examiner has made three rejections of the claims and one objection to the claims. Applicants respectfully offer the following remarks concerning each of these elements of the Office Action.

III. Rejection under 35. U.S.C § 102(b) Is Traversed

In section 5 of the Office Action at pages 3-4, the Examiner has rejected claims 50-53 under 35 U.S.C. § 102(b) as anticipated by Lee *et al.*, Science 239: 1288-1291 (1988) (of record as Doc. No. AT14; hereinafter "Lee"). Applicants respectfully traverse this rejection.

As a preliminary matter, the Examiner has based this rejection on the same points that were made in the Office Action dated March 5, 2004. In their reply submitted July 6, 2004, Applicants provided specific grounds of rebuttal of each of these contentions, demonstrating why the anticipation rejection was legally and factually baseless. However, instead of specifically rebutting Applicant's arguments in the present Office Action, the Examiner has

simply reiterated the points made in the previous Office Action. Such an approach does not advance prosecution.

Moreover, Applicants respectfully remind the Examiner that "[w]here the applicant traverses any rejection, the examiner should, if he or she repeats the rejection, take note of the applicant's argument and answer the substance of it." MPEP § 707.07(f) (February 2003). Clearly, this guidance of the MPEP has not been followed in issuing the present anticipation rejection. Based solely on this reason, Applicants respectfully contend that the present anticipation rejection under 35 U.S.C. § 102(b) is improper, and should be reconsidered and withdrawn in its entirety. However, should the Examiner not be inclined to do so, Applicants offer the following additional remarks regarding this rejection.

In making this rejection, the Examiner contends that Lee discloses the purification of porcine and murine tetrameric uricases that contain at least about 90% tetrameric uricase because the reference mentions that porcine and murine urate oxidase were "purified to homogeneity." *See* Lee at page 1289. The Examiner thus interprets a "homogeneous" preparation of uricase in Lee to be 100% in the tetrameric form. See Office Action at page 3, final (partial) paragraph. Applicants respectfully disagree with this interpretation for at least the following reasons.

First, Lee does not expressly disclose the purification of *tetrameric* mammalian uricase as recited by the claims of the present application. This reference only indicates *in passing* that porcine liver and murine urate oxidase were purified to homogeneity. This reference does *not* indicate that at least about 90% of the "purified" uricase was in a tetrameric form. Indeed, the reference does not indicate in *what* form the "purified" uricase was, let alone that at least about 90% of it was in a tetrameric form.

Second, despite the Examiner's assertion, "purified to homogeneity" does not mean that at least about 90%, or even 100%, of the uricase is in a tetrameric form. As the present specification clearly teaches at page 16, lines 5-16, purified preparations of natural and recombinant uricase usually contain a *mixture* of forms of the enzyme, in addition to the tetrameric form. The estimated percentage of the non-tetrameric form of the enzyme present in such "purified" preparations varies from more than 10% to about 80%. *See id.* Hence, without specifically purifying their uricase preparations to enrich for the tetrameric form over all other forms, the authors of Lee would not be expected to have produced a uricase preparation in which at least about 90% of the uricase is in a tetrameric form. Thus, as one of ordinary skill would readily appreciate, Lee does not disclose the production of mammalian uricases having the characteristics recited in the present claims.

Finally, and perhaps most importantly, it must be noted that the method employed and cited by Lee for assessing the homogeneity of the murine urate oxidase preparations disclosed in that reference confirms that Lee is analyzing *monomeric* subunits of uricase rather than the tetrameric form of the enzyme. *See* T.G. Conley and D.G. Priest, "Purification of Uricase from Mammalian Tissue," *Preparative Biochemistry* 9:197-203 (1979) (hereinafter "Conley"). Conley (and therefore Lee, *citing* Conley at page 1289, 2nd column) used SDS/PAGE to analyze the uricase, reporting that the "enzyme is homogeneous upon polyacrylamide gel electrophoresis in the presence of sodium dodecyl sulfate." *See* Conley at p. 201. As one of ordinary skill would immediately recognize, the conditions of SDS/PAGE employed by Conley (and therefore Lee) *dissociate* any uricase tetramers that might be present into the smaller 32-33 kDa *monomeric* subunits. As disclosed in the present specification at page 16, lines 5-7, tetrameric uricase is a 140 kDa protein. Hence, Conley (and therefore Lee) clearly is identifying *monomeric* forms of

uricase, rather than tetrameric forms of uricase. Lee does not even mention purifying a tetrameric form of uricase, disclosing only the purification of uricase monomers. Thus, it is clear from the Conley reference that Lee, in disclosing "purification to homogeneity" of porcine and murine uricases, is preparing uricase *monomers* and *not* uricase preparations in which at least about 90% of the uricase is tetrameric, as is presently claimed.

Under 35 U.S.C. § 102, a claim can be anticipated only if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). In addition, a claim can be anticipated by a publication only if the publication describes the claimed invention with sufficient enabling detail to place the public in possession of the invention. *See In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985); *see also PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter."). The Examiner has pointed to no express disclosure in Lee that would support the Examiner's statement that the "homogeneous preparations of porcine or murine tetrameric uricase comprises the at least about 90% tetrameric form of mammalian uricase claimed." Office Action at pages 3-4. As noted above, Lee does not expressly disclose the production of a uricase in which at least about 90% of the uricase is in a tetrameric form, and indeed discloses only the production of *monomeric* uricase.

If instead the Examiner is basing this rejection upon the possible inherent disclosure of the claimed uricases in Lee, Applicants respectfully disagree with this approach. To rely on an inherency argument, "the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows

from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (PTO Bd. Pat. App. Int. 1990) (emphasis in original). This burden has not been met in the present case, since the Examiner has pointed to no disclosure in Lee, nor any sound scientific reasoning, that uricases containing at least about 90% tetrameric uricase "necessarily flow" from the disclosure in Lee. Indeed, as discussed in detail above, the present specification clearly shows that by preparing uricases according to the methods of Lee, one of ordinary skill at best would succeed in preparing uricases that contain *less* than about 90% tetrameric uricase. Indeed, the methods of Lee would result in a uricase preparation in which most, if not all, of the uricase was in a *monomeric*, not tetrameric, form. Thus, any reliance upon inherent anticipation by Lee is factually and legally unfounded.

Accordingly, Lee does not expressly or inherently disclose the presently claimed invention. Hence, under *Kalman*, this reference cannot support a rejection under 35 U.S.C. § 102(b). In view of the foregoing remarks, Applicants respectfully assert that Lee does not anticipate claims 50-53. Reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(b) over Lee therefore are respectfully requested.

IV. Rejection under 35 U.S.C. § 103(a) Is Traversed

In section 6 of the Office Action at pages 4-5, the Examiner has rejected claims 74-76 under 35 U.S.C. § 103(a) over Lee in view of Caput *et al.*, U.S. Patent No. 5,382,518 (Doc. "A" cited on the Form PTO-892; hereinafter "Caput"). Applicants respectfully traverse this rejection.

In proceedings before the Patent and Trademark Office, the examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223

USPQ 785, 787-88 (Fed. Cir. 1984). In order to establish a *prima facie* case of obviousness, all of the elements of the claims must be taught or suggested by the prior art. *See In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Moreover, the Examiner can satisfy the requisite burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). There is no basis for concluding that an invention would have been obvious solely because it is a combination of elements that were known in the art at the time the invention was made. *See Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 (Fed. Cir. 1995). Instead, what is needed is a reason, suggestion, or motivation in the prior art that would motivate one of ordinary skill to combine the cited references, and that would also suggest a reasonable likelihood of success in making or using the claimed invention as a result of that combination. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). In the present case, the Examiner's burden has not been satisfied.

Claim 74 (and thus the remaining claims depending therefrom) is drawn to a pharmaceutical composition for lowering uric acids levels in a body fluid or tissue where the composition comprises an isolated tetrameric mammalian uricase and a pharmaceutically acceptable carrier, wherein at least about 90% of the uricase is in the tetrameric form. Applicants reiterate and incorporate by reference herein the remarks made above with respect to Lee. Lee does not disclose, suggest, or otherwise contemplate an isolated tetrameric mammalian uricase, wherein at least about 90% is in the tetrameric form. By extension, then, Lee can not disclose pharmaceutical compositions comprising such uricase preparations. Therefore, Lee is seriously deficient as a primary reference upon which to base a *prima facie* case of obviousness.

These deficiencies are not cured by the disclosure of Caput. Caput does not disclose, suggest, or otherwise contemplate isolated tetrameric mammalian uricases and a pharmaceutically acceptable carrier, wherein at least about 90% of the uricase is in the tetrameric form. Therefore, the disclosure of Lee, alone or in combination with that of Caput, does not disclose, suggest or contemplate pharmaceutical compositions for lowering uric acid levels in a body fluid or tissue where the composition comprises an isolated tetrameric mammalian uricase and a pharmaceutically acceptable carrier, wherein at least 90% of the uricase is in the tetrameric form.

Applicants have established above that the references cited by the Examiner fail to teach all of the elements of the present claims. Therefore, it follows that a combination of the disclosures of these references would *not* lead one of ordinary skill in the art to Applicants' claimed invention. Notwithstanding this fact, Applicants also contend that neither the references themselves, nor the knowledge generally available to those of ordinary skill in the art, provide a suggestion or motivation to modify the cited references or to combine disclosures of the cited references.

The Examiner states that one of ordinary skill in the art at the time of invention would have been motivated to:

> substitute *Aspergillus* uricase...with the mammalian uricase ... in developing pharmaceutical compositions for lowering uric acid in body fluid of man ... [because] man belongs to the class of mammals and a uricase originating from a mammalian species will be more compatible and perhaps more effective in lowering uric acid in man.

Office Action at pages 4-5. Applicants respectfully disagree with these contentions. To the contrary, a person of ordinary skill in the art would *not* have been motivated to use mammalian

uricase as a substitute for *Aspergillus* uricase simply because "man belongs to the class of mammals," for at least two reasons: immunogenicity and insolubility.

First, as pointed out in the specification, enzymes based on the deduced amino acid sequences of uricases from mammals, including pig and baboon, have been shown not to be suitable candidates for human clinical use due to problems of immunogenicity. Specifically, since humans do not produce uricase (*see* Specification at page 1, lines 24-26), uricases from *any* other species, including other mammals, would be recognized as foreign by the human immune system and would be rapidly cleared or, in some hypersensitive humans, may lead to anaphylactic reactions (*see* Specification at page 2, lines 1-7 and 24-28). In either case, such immunogenicity would render the unmodified mammalian uricases virtually ineffective as human therapeutic agents. For this reason alone, then, one of ordinary skill would not have been motivated to use uricases from other mammalian species instead of *Aspergillus* uricase.

Second, as also pointed out in the specification, enzymes based on the deduced amino acid sequences of uricases from mammals, including pig and baboon, have been shown not to be suitable candidates for human clinical use due to problems of insolubility. Specifically, it is known that unmodified uricases obtained from mammals "are nearly insoluble in solvents that are compatible with safe administration by injection." Specification at page 2, lines 18-19 and 24-28. Thus, even apart from the immunogenicity problems noted above, one of ordinary skill would not have been motivated to use uricases from other mammalian species instead of *Aspergillus* uricase due to the insolubility of these unmodified uricases at physiological pH.

Hence, the use in humans of mammalian uricases instead of *Aspergillus* uricase would not be expected to overcome the immunogenicity problems associated with the latter, and would instead lead to a second problem: enzyme insolubility at physiological pH. Therefore, given

these problems associated with the use of mammalian uricases in humans, one of ordinary skill in the art would not have been motivated to make the Exminer's proposed substitution of mammalian uricase for *Aspergillus* uricase to achieve the presently claimed invention. Indeed, just the *opposite* is true -- one of ordinary skill would more likely have been motivated *away* from using mammalian uricases in treating humans, since attempts to use unmodified mammalian uricases in humans leads to additional problems beyond those seen with the use of *Aspergillus* uricase. Thus, it is simply incorrect to assume that because humans are mammals, the use of uricases from other mammalian species might somehow be "more compatible" or "more effective" in humans *per se*.

In addition, the apparent basis for this rejection appears to misconstrue the standard for obviousness and the source from which the required motivation must arise in order for a *prima facie* case of obviousness to be established. Applicants respectfully remind the Examiner that the requisite motivation for establishing a *prima facie* case of obviousness *must* be found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *See In re Kotzhab*, 217 F.3d 1365, 55 USPQ2d 1313 (Fed. Cir. 2000). Moreover, the mere fact that an advantage *might* be realized by combining reference teachings does not mean that a skilled artisan would have been motivated to do so. *See In re Mills*, 916 F.2d 680,682, 16 USPQ2d 1430, 1432 (Fed. Cir. 1992) (Although a prior art device "may be capable of being modified to run the way the apparatus is claimed, there must be a suggestion or motivation in the reference to do so.").

In the present case, rather than pointing to anything specific in the references or in the general knowledge of those skilled in the art, the Examiner has simply asserted that the mammalian uricase of Lee can be combined with the pharmaceutical compositions of Caput to

provide a more compatible and effective pharmaceutical composition. This assertion clearly misses the point, and does not provide the requisite motivation to combine the cited references. There is absolutely *nothing* in Lee or Caput that would have motivated one of ordinary skill in the art to have produced pharmaceutical compositions for lowering uric acids levels in a body fluid or tissue where the composition comprises an isolated tetrameric mammalian uricase and a pharmaceutically acceptable carrier, wherein at least about 90% of the uricase is in the tetrameric form. Simply put, for reasons discussed in detail above, neither Lee nor Caput disclose the production of a uricase, from *any* species, that is at least about 90% in the tetrameric form. Again, uricase homogeneity does not *a priori* mean the uricase is 100% in a tetrameric form-- instead, it is more likely that such a preparation is predominantly in the monomeric form. Hence, neither Lee not Caput provides the requisite teachings or suggestions to support the rejection.

Having failed to demonstrate support for the rejection in Lee or Caput, the Examiner instead appears to attempt to base this rejection on an inherent "motivation" present in those of ordinary skill in the art. However, the Examiner has pointed to no acceptable objective evidence or sound scientific reasoning that would provide such motivation. Instead, the Examiner appears to *assume* that such motivation exists in the "general knowledge," without providing any basis for such an assumption. As discussed above, the requisite motivation must be found either in the prior art or in knowledge that is generally available to those of ordinary skill in the art; a baseless *assumption* of such knowledge is legally impermissible under *Fine* and *Kotzhab*. Moreover, as the Federal Circuit has held:

> [t]he range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not "evidence."

In re Dembiczak, 175 F.3d 994, 999 (Fed. Cir. 1999) (citations omitted). Since the Examiner has provided no actual evidence to support the conclusory statement that Lee and Caput in combination render the present invention obvious, Applicants respectfully assert that a *prima facie* case of obviousness has not been established. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103(a).

V. Rejection under 35 U.S.C. § 101 Is Traversed

In section 7 of the Office Action at page 5, the Examiner has provisionally rejected claims 50-56, 58-59 and 74-76 under 35 U.S.C. § 101 as allegedly claiming the same invention as that of claims 1-9 of copending Application No. 09/501,730 (issued on August 31, 2004, as U.S. Patent No. 6,783,965 (the '965 patent)). Applicants respectfully traverse this rejection.

The test for whether the "same invention" is being claimed twice is whether a claim in the application could be literally infringed without literally infringing a corresponding claim in the patent. If it could be, the claims do not define the same invention. *See In re Hallman*, 655 F.2d 212, 210 USPQ 609 (C.C.P.A. 1981). In the present case, there are multiple embodiments of the invention that fall within the claims of the present application but fail to literally infringe claims 1-9 of the '965 patent. For example, an embodiment that provides an isolated mammalian uricase comprising 95% of the tetrameric form and 5% of aggregates larger than octamers would literally infringe the claims of the present application but would not literally infringe claims 1-9 of the '965 patent. Therefore, since the claims of the present application could be literally infringed without literally infringing the claims in the '965 patent, the two sets of claims do not define the same invention.

In view of the foregoing remarks, Applicants respectfully assert that claims 1-9 of the '965 patent do not encompass the "same invention" as claims 50-56, 58-59 and 74-76 of the present application. Therefore, reconsideration and withdrawal of the rejection under 35 U.S.C. § 101 are respectfully requested.

VI. Objection to Claim 57

In section 8 of the Office Action at page 5, the Examiner has objected to claim 57 for being dependent upon a rejected base claim. However, in light of the remarks made above, it is believed that the rejections of Claims 50-56, 58, 59 and 74-76 have been overcome and therefore, the objection to claim 57 has been obviated. Accordingly, reconsideration and withdrawal of this objection are respectfully requested.

VII. Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply, and allowance of all pending claims, are respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Brian J. Del Buono
Attorney for Applicants
Registration No. 42,473

Date: Nov. 2, 2004

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

309750